Endothelium-dependent and endothelium-independent vasodilator response of left and right internal mammary and internal thoracic arteries used as a composite Y-graft

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Abstract

Objective: The manner in which a blood vessel is used as a coronary graft may be important in maintaining a viable and functional endothelial lining. Composite internal thoracic arteries (ITAs) in a Y-graft configuration are characterized by the connection of an in situ left ITA with preserved innervation and lymphatics and of a free semi-skeletonized right ITA. Methods: To determine whether endothelial function differs between left and right ITA segments in a Y-graft configuration, 11 patients were studied 3 years after surgery. The endothelium-dependent vasodilator substance P was selectively infused (1.4–22.4 pmol min⁻¹) in doubling dose increments in the ostium of ITA Y-grafts. A maximal endothelium-independent vasodilatory response was then obtained by intragraft infusion of 2 mg isosorbide dinitrate (ISDN). Biplane angiograms obtained at 3-min intervals using an automated contrast injection system with fixed preset volume and pressure parameters were analyzed offline using a quantitative analysis system (CAAS, Pie Medical). Results: A similar dose-dependent vasodilatory response to substance P was observed in the left and in the right ITA. No difference in maximal endothelium-dependent response to substance P (7.4 ± 4.3% in the left ITA and 8.1 ± 5.3% in the right ITA) or in maximal endothelium-independent response to ISDN (12.2 ± 4.4% in the left ITA and 10.6 ± 8.1% in the right ITA) was observed. Conclusions: The endothelium-dependent and the endothelium-independent vasodilator capacity of the two branches of a Y-graft ITA configuration appear similar 3 years after bypass surgery. This suggests that the preservation of the ITA pedicle does not significantly affect basal vasomotor tone, long-term endothelial function, or vasodilator reserve.

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Keywords: Surgery; Bypass; Coronary disease; Endothelial function; Internal thoracic artery

1. Introduction

The superiority of the internal thoracic artery (ITA) over venous grafts has been demonstrated by several long-term follow-up studies [1,2]. The superior patency of the ITA is thought to result from a better capacity of the endothelium to release dilator substances, particularly nitric oxide (NO) [3,4] and to protect the graft against vasospasm and atherothrombosis [5]. Observational studies suggest that bilateral ITA (BITA) could improve long-term survival of patients when compared with the association of a single ITA implanted into the left anterior descending (LAD) coronary artery with one or several saphenous vein grafts (SVGs). A limitation of the use of BITA as in situ left and right grafts is the length of the right ITA that limits the possibilities to reach distal branches of the left circumflex system. To allow more extensive revascularization of the left coronary artery system using segments of ITA of sufficient diameter, Barra and Tector [6,7] have proposed the use of composite Y- or T-grafts. In these configurations, a free proximal segment of the right ITA is connected proximally to the in situ left ITA and distally to one or several branches of the left circumflex. In contrast to the free right ITA segment, the innervation and the lymphatic drainage of the pedicled left ITA are preserved.

Uncertainties remain whether section and the resulting denervation of the right ITA could affect basal vasomotor tone, vasodilator reserve, or endothelial function. The present study was designed to compare the endothelium-dependent and endothelium-independent vasodilator response of the two distal branches of composite Y-grafts. Substance P was used as a pure endothelium-dependent vasodilator stimulus and isosorbide dinitrate was used to elicit a full endothelium-independent dilator response.


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2. Methods

2.1. Patients

Between 2003 and 2007, 210 patients underwent non-emergent coronary artery bypass surgery using the left ITA to the LAD artery and the right ITA to the circumflex territory in a Y-composite graft configuration. Of these, 146 patients consented to a 3-year postoperative follow-up angiographic study [8]. The criteria for inclusion in the substance P study protocol were the absence of major tortuosities of the graft, patency of all anastomoses with a good runoff flow to the grafted arterial segments, the absence of severe wall motion abnormality in the perfusion zone, and the possibility to selectively cannulate the left internal mammary artery (LIMA) with the angiographic catheter. Exclusion criteria were renal insufficiency, peripheral vascular disease, and history of neurologic events. Of the 146 patients undergoing follow-up angiography, 11 patients benefited from a more complete examination with substance P protocol.

Mean number of anastomosis per patient with the left ITA and right ITA was 1.5 and 2.4, respectively. Patients’ characteristics are given in Table 1. At time of evaluation, patients were asymptomatic and did not show evidence of myocardial ischemia during maximal exercise testing. Preoperative coronary lesions are detailed in Table 2.

The study protocol was approved by the Ethics Committee of our institution. All patients gave informed consent at the time of bypass surgery and before the angiographic investigations.

2.2. Study protocol

Patients underwent cardiac catheterization by the standard femoral approach. To avoid any vasoactive drug interference, all patients interrupted all vasoactive medications 24 h before the systematic 3-year angiographic study. Selective catheterization of the ostium of the left ITA was achieved by using a 5-F guiding catheter without side holes. Two perfusion lines were connected to the catheter placed in the ostium of the LIMA, the first containing Substance P (14 pmol ml⁻¹), and the second 9% saline serum.

All angiograms were obtained in biplane, by injection of a non-ionic contrast agent (Iohexol 350 mg 100 ml⁻¹) using an automated injection system with a fixed pre-set volume and pressure. A couple of angiographic projections best displaying both IMA grafts and coronary arteries (LAD artery and circumflex artery) were selected from the diagnostic films; these projections and the positions of the patient and of the X-ray system were not altered during the entire course of the study. After the baseline angiogram, substance P was infused for 3-min periods starting at a dose of 1.4 pmol min⁻¹, rising by doubling increments to 22.4 pmol min⁻¹ (Table 3). The flow of saline was simultaneously adapted to maintain a constant flow rate of 3.0 ml min⁻¹ in the angiographic catheter throughout the study. Biplane angiograms were obtained during the last seconds of each 3-min period. On completion of the substance P infusion, a bolus dose of 2 mg isosorbide dinitrate was given and a final angiogram was taken.

2.3. Data analysis

Angiograms were quantitatively analyzed using the CAAS II system (Pie Medical, Maastricht, the Netherlands) as previously described [9]. The diameter of the chosen vascular segment, identified by anatomical landmarks, was measured in the two orthogonal views at the 7 study period and the mean value of these measurements was considered for statistical analyses. Four different arteries were analyzed: left ITA and right ITA immediately distal to the site of the Y connection and a segment of the grafted circumflex and LAD coronary artery.

2.4. Statistical analysis

Data are expressed as mean ± 1 SD. Paired samples t-tests were used to compare changes in lumen diameters expressed

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Table 1. Patients characteristics.

<table>
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<th>Patient No.</th>
<th>Mean age (years)</th>
<th>Gender (male)</th>
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<td></td>
<td>55 ± 10</td>
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Table 2. Second graft and preoperative coronary stenosis.

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<th>DG % Stenosis</th>
<th>OM1 % Stenosis</th>
<th>OM2 % Stenosis</th>
<th>PLA % Stenosis</th>
<th>PDA % Stenosis</th>
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Mean % stenosis: 80 | 86 | 83 | 80 | 80 | 88

Abbreviations: LAD: left anterior descending coronary artery; DG: first diagonal branch of the left anterior descending coronary artery; OM1 and OM2: first and second marginal branches of the left circumflex coronary artery; PDA: posterior descending artery; RITA: right internal thoracic artery; SVG: saphenous vein graft.
in absolute values or in percentage of basal diameter of the right IMA and LIMA, and circumflex and IVA. Due to the small sample size, results were validated with the Wilcoxon signed rank sum test, a non-parametric version of a paired samples t-test. P-value less than 0.05 was considered to be statistically significant.

3. Results

At baseline, the diameters of the left ITA (mean: 2.2 ± 0.6 mm) and the right ITA (2.6 ± 0.6 mm) were similar (P = 0.14) and significantly larger than the diameter of the corresponding grafted coronary segment (L circumflex: 1.5 ± 0.3 mm and LAD: 1.4 ± 0.3 mm). Changes in luminal diameters of the right and left ITA are reported in Fig. 1. A similar dose-dependent dilator response to substance P is observed in both types of grafts, up to 107.4 ± 4.3% of basal diameter in the left ITA and 108.1 ± 5.3% of basal diameter in the right ITA. Selective intragraft injection of isosorbide dinitrate induced a further dilator response, the maximal vasodilation being similar in the left (12.2 ± 4.4%) and the right (10.6 ± 8.1%) ITA. Grafted coronary segments responded to substance P in a dose-dependent manner (Fig. 2) and dilated further after isosorbide dinitrate, the maximal dilation after nitrates being significantly larger than that observed for ITA grafts.

4. Discussion

The endothelium-dependent response to substance P and the maximal endothelium-independent response to isosorbide dinitrate of the two branches of a Y-graft ITA configuration appear similar 3 years after bypass surgery. This suggests that preservation of an in situ ITA is not a prerequisite to preserve basal vasomotor tone, long-term endothelial function, or vasodilator reserve in the long term.

The ITA has peculiar biological features that render this artery an almost ideal conduit for surgical myocardial revascularization. Biological and morphological studies have demonstrated how this artery is protected from the development of atherosclerosis even in patients with severe coronary artery disease. These intrinsic biological characteristics have been translated in far better angiographic results than all other conduits used for coronary artery bypass grafting [1,2]. He et al. [10] endeavoring to find an explanation for the ITA patency superiority investigated and compared NO release and endothelium-derived hyperpolarizing factor (EDHF)-mediated hyperpolarization for ITA and radial artery. They found that the basal and stimulated releases of NO and EDHF-mediated hyperpolarization in the IMA are significantly greater than that in the radial artery. They concluded that, lower capacity of NO release may contribute to the susceptibility of the radial artery to the perioperative vasospasm, and may have an impact on the
long-term graft patency. Moreover, Mangoush et al. [11] studied the antioxidant properties of blood vessels and how they contribute to their performance and patency when used as a bypass conduit. They compared the ability of the radial artery to generate superoxide and assessed its antioxidant protective capacity with that of the ITA. They found that the radial artery is less equipped with an antioxidant protective mechanism compared with the ITA.

The adoption of composite thoracic artery conduits (as Y configuration) has been advocated by several authors to maximize the benefits of thoracic artery revascularization [12,13]. Therefore, bilateral use of the ITA for grafting with the right internal mammary artery used as a ‘free’ graft may result in improved graft survival. Our group has demonstrated in a prospective randomized angiographic and clinical study comparing in situ and composite Y ITA grafting that there were no significant differences in terms of major adverse cerebro-cardiovascular event and patency up to 19 months postoperatively [8]. However, even if the total number of anastomosis per patients was similar, there was a significant difference in the number of ITA anastomoses between the two groups (3.2 in the BITA Y vs 2.4 in the ITA in situ, P < 0.01). As of today, there are no series reporting the long-term clinical benefit of such increases of anastomoses with the use of the BITA Y configuration. In a recent study, Rankin et al. [2] found excellent 20-year survival with in situ BITA grafting. The cumulative percent of repeat revascularization at 20 years is 40.7% (percutaneous coronary intervention 35.7% and redo 5%). Considering the higher attrition rate of venous graft compared with ITA graft, and the larger use of venous anastomoses in the BITA in situ group, we could speculate that the adjunction of this significant number of ITA anastomosis could, in the long term, decrease the number of late re-interventions in the BITA Y group.

Kushwaha et al. [14] have studied the vasodilatation of free and in situ ITA grafts in response to endothelial-dependent and endothelium-independent mechanisms. They found that the dilatory ability of an ITA implanted on the aorta or used in situ is comparable after coronary artery bypass surgery. Thus, the dilatory ability of the right IMA as a free graft implanted on the aorta does not appear to be affected by transection of this vessel near its point of origin; and denervation, as well as the loss of the vasa vasmorum and lymphatics, does not significantly affect endothelial function of the free IMA graft [10,13]. Our data are consistent with these findings and confirm the absence of alteration in these dilatory mechanisms of the free right ITA graft when used as a composite Y graft.

4.1. Study limitations

We were not able to find a significant difference of vasomotion between ITAs or coronary arteries. This does not mean, however, that there is no difference. This negative result might be a consequence of the small sample size of patients.

References


Appendix A. Conference discussion

Dr G. Wimmer-Greinecker (Bad Bevensen, Germany): I would like to ask you three questions. You have only studied 11 patients. Were those patients randomly picked? Because these were 11 out of 146. Did the other 135 patients have tortuositities, did they have a stenosis or were they occluded? Do you know the outcome of those 135 patients?
The second question is: you say your major concern would be denervation or disconnection of the lymphatic system. If that is your major concern, why did you measure immediately after the anastomosis? I would at least assume that after three years there could be a re-innervation at this site. So if you had measured at a later stage, maybe this effect would have been less.

And the last question relates to the use of semi-skeletonized grafts. Of course this is speculation, but would you think that in a totally skeletonized graft, the results would be different? People doing Y or T grafts, usually do completely skeletonize their arteries. Will your findings influence your strategy in the future?

Dr Glineur: Concerning the first question, why these 11 and not others. As I said, we have done systematic six-month and three-year angiographic follow-up in our prospective randomized trial. While reviewing the six-month angiography, I had the feeling that there was a lot of controversy concerning the composite Y-grafting. Therefore I thought that at the three-year angiography follow-up, I had to find something showing that the free right mammary vaso-reacts exactly as in situ left mammary. When we started the three-year angiographic follow-up, we looked at, let’s say, the ideal patients, meaning no dysfunction of the left ventricle, all with patent anastomoses. The major limitation of such a protocol is that it needs to have an easy catheterization of the ostium of the left mammary, because it is important to be perfectly stable during the injections. These 11 patients are the first 11, let’s say easy patients to cannulate the ostium in order to have a stable catheter during all 25 minutes of the study. It is very important that the catheter moves, it means that you have to modify the biplane angiograms, meaning that everything has to be started again.

The second question, why did we measure the diameter just after the Y-graft anastomosis? Well, it is mainly an anatomical reason. It is easier to find anatomical landmarks just after the Y-graft in both orthogonal views in order to be sure to measure the same coronary segment. That is the reason why we measure it there.

And regarding your last question concerning the skeletonization, well, I think that it is totally equal if you completely skeletonize your artery. Of course, if you have haematomas everywhere on the ITA surface, perhaps it will be different, but if you have a normal skeletonized mammary wall, I think it is equal; we will obtain the same results.

Dr W. Chong (Brunei): Just two questions. One is, your catheter, when you stabilized it, was it at the ostium of the left internal mammary artery? If so, when you give your drug, how do you ensure that an equal proportion of drug goes down the LIMA and the free RITA? Obviously the LIMA which is grafted to the LAD has a larger territory. On that assumption, the majority of the drug would have gone down the LIMA.

Dr Glineur: So, exactly, the angiographic catheter was introduced just at the entry of the LITA. There is always a question of what goes where, I totally agree with you, but this does not really change the fact that the blood goes into the right mammary, and into the left mammary, in proportion to the runoff of each territory. So I don’t think that it will affect the vasomotion of both mammaries.

Dr Chong: But it does if you assume that the majority of the drug goes down into the LAD.

Dr Glineur: Well, if that were true there would be a steal phenomenon, and we have proven that there is no steal phenomenon when using Y-grafting.

Dr Chong: So you are assuming that an equal proportion goes down each graft?

Dr Glineur: I think the blood going into both sides of the Y-graft is proportional to the runoff.

Dr Chong: Because the LAD obviously has a bigger runoff than the circumflex.

Dr Glineur: Well, it is not necessarily true. It depends on the number of anastomoses you have realised on the lateral wall and on the inferior wall of the heart. For example, if you have grafted three marginals and the PDA of an occluded right coronary artery, you clearly have the same runoff on the lateral and posterior wall as on the LAD.

Dr Chong: Now, the second question is, between your injection of substance P and the ISDN, was there a washout period?

Dr Glineur: Yes, of course. There was something like a three-minute washout period.